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Accepted Manuscript

Neonatal Listeriosis in the UK 2004-2014

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Summary

Objective

To define the clinical features and outcomes of neonatal listeriosis, and identify the maternal risk factors to seek scope for improvement.

Methods

Neonatal listeriosis was identified prospectively from a United Kingdom neonatal infection surveillance network (neonIN) between 2004 and 2014. The participating neonatal units completed a study-specific proforma.

Results

The incidence of neonatal listeriosis was 3.4 per 100,000 live births. Of the 21 cases identified, 19 were confirmed with a median gestational age of 33 weeks and a median birth weight of 1960g. The majority had clinical features (95%, 18/19), presented within the first 24 hours (95%, 18/19), and received penicillin empirically (94%, 18/19). The neonatal case-fatality rate was 21% (24% if probable cases were included). A proportion of mothers were investigated (60%, 12/18) and diagnosed with listeriosis (58%, 7/12); 32% (6/19) were treated with antibiotics but only 33% (6/12) included penicillin.

Discussion

Despite its rarity and the prompt and appropriate use of antibiotics neonatal listeriosis has a high case-fatality rate. There is room for improvement in the adherence to the national guidance in the choice of empiric antibiotics for puerperal sepsis, which would target listeriosis. Strategies should be in place to prevent pregnancy-associated listeriosis in higher risk population.

Introduction

Listeria monocytogenes is a Gram-positive bacillus. *L. monocytogenes* causes listeriosis, an infection predominantly transmitted through the consumption of contaminated food. Recent estimates suggest that listeriosis is the most common cause of food-related deaths in the UK (130 deaths in 2005) [1]. The incidence of listeriosis in pregnancy is 12 per 100,000, compared with a rate of 0.7 per 100,000 in the general population [14].

For an antibiotic to be effective against *L. monocytogenes*, the antibiotic must penetrate into the host cell, maintain a high concentration and bind to the penicillin-binding protein (PBP), which causes cell death. Penicillin, amoxicillin and ampicillin have been used most extensively in the treatment of listeriosis as these drugs block several PBPs and do penetrate intracellularly. Some in-vitro studies also suggest a synergistic effect when gentamycin is added to the treatment regimen [9]. Studies in Denmark and Northern Italy found *L. monocytogenes* human isolates to be susceptible to ampicillin, amoxicillin, benzylpenicillin, meropenem, erythromycin and gentamicin [12,13]. *L. monocytogenes* is intrinsically resistant to broad-spectrum cephalosporin antibiotics, which are commonly used in treatment of bacterial infections [6].

Neonatal listeriosis occurs via congenital infection. In the UK, it is the third most common cause of early-onset neonatal infection [3] and the fourth most common cause of early-onset neonatal meningitis [7]. It manifests commonly in the first 24 to 72 hours of life (62% of cases) [3]. Early-onset neonatal listeriosis can manifest as bacteraemia, meningitis and less commonly pneumonia. Late-onset neonatal listeriosis is most commonly associated with meningitis [2].

Neonatal listeriosis is associated with high case fatality rates. In the UK between 1967 and 1985, 248 out of 722 cases of human listeriosis (34%) were associated with pregnancy of which 42 cases resulted in intrauterine deaths (19%) and 47 in neonatal deaths (35%), with an overall case fatality rate of 50% [4].

This study aims to define the clinical features, risk factors and outcomes of neonatal listeriosis in a UK neonatal infection network over a period of 11 years.

Materials and Methods

Cases of neonatal listeriosis were prospectively identified between January 2004 and December 2014 through neonIN, a neonatal infection surveillance network (www.neonin.org.uk). The contributing centres voluntarily collect data on culture-positive neonatal infections onto the web-based research database, which is also crosschecked with laboratory records to ensure validity and quality.

All neonIN centres in the UK contributing data within the study period were contacted and requested to complete a study-specific proforma for additional information (maternal and neonatal demographics, risk factors, clinical features, antimicrobial treatments and outcomes) on all cases of neonatal listeriosis. Cases were categorised as confirmed (defined as a case when *L. monocytogenes* was isolated from a normally sterile culture site of the neonate) and probable (defined as a case when *L. monocytogenes* was isolated from a normally sterile culture site of the mother, but no bacteria is isolated from a normally sterile culture site of the neonate who is clinically felt to be septic), and were analysed separately.

The data was analysed on Microsoft Excel 2010. Comparisons were made with chi-square test for the data on ethnic distribution. The incidence of neonatal listeriosis was calculated using the cumulative hospital live births as a denominator.

NeonIN received ethics approval from the London-Surrey Borders Research Ethics Committee in 2005 (05/Q0806/34) and in 2010. Each participating centre received separate approval from their local ethics committees prior to joining the network.

Results

Over the 11-year period, 18 neonatal units reported 21 cases of neonatal listeriosis. The overall incidence was 3.4 per 100,000 live births. Of the 21 cases identified, 19 were confirmed and 2 were probable. An overview of the maternal and neonatal results can be seen in Table 1 and Table 2 respectively.

Maternal Results

The median maternal age was 29 years (range 21-42, IQR 9). Of the 14 cases recorded (13 in England and 1 in Scotland), 50% were Caucasians, 29% Afro-Caribbeans and 21% Asians (Table 1). When comparing the data on ethnic distribution from the neonIN-participating centres in England against the Office for National Statistics population data in England, we identified a disproportionately high representation of Asian and Afro-Caribbean women in our sample ($p < 0.001$) [5].

Clinical features were present in 95% (20/21) of mothers antenatally with onset of preterm labour being the most common. Complications during labour occurred in 62% (13/21). Of the 20 cases recorded, 60% (12/20) had blood cultures performed of which 58% (7/12) were positive for *L. monocytogenes*. Overall, 55% (11 out of 20 recorded cases) were not diagnosed with maternal infection. Of the 19 cases recorded, 32% (6/19) received antibiotics pre-delivery; one-third (2/6) included penicillin and two-thirds (4/6) included cephalosporins (Table 1).

Neonatal Results – Confirmed Cases

Of the 19 confirmed cases of neonatal listeriosis, the median gestational age was 33 weeks (27-38 weeks, IQR 5 weeks), the median birth weight was 1960g (1070-3210g, IQR 1002g), 90% (17/19) were born at less than 37 gestation weeks, 63% (12/19) had a birth weight of less than 2500g and 21% (4/19) had a birth weight of less than 1500g (Table 2).

Clinical features were present in 95% (18/19) of neonates with respiratory distress being the most common, and 95% (18/19) of the neonates presented within the first 24 hours. Meconium stained liquor was present in 62% (13/19). Cardio-respiratory support was required in 84% (16/19). In terms of diagnosis, 90% (17/19) were diagnosed with septicaemia, 21% (4/19) with meningitis and 5% (1/19) with pneumonia. The one (5%) neonate who presented after the first 24 hours did so at 10 days of age with pyrexia and was diagnosed with meningitis (Table 2).

In terms of treatment, 94% (17/18) of neonates with early-onset infection received penicillin empirically and 1 (6%) received a cephalosporin. Antibiotics were administered within 1 hour of birth in 67% (8/12), between 1 to 2 hours after birth in 17% (2/12) and more than 2 hours after birth in 17% (2/12). The neonate with late-onset listerial meningitis also received a penicillin as part of the empiric treatment (Table 2). The duration of penicillin treatment was variable (Table 2); of the 3

neonates with meningitis, 2 completed a 21-day course and 1 a 50-day course, and of the 10 with septicaemia, 7 completed a 21-day and 3 a 14-day course.

Looking at outcome, 21% (4/19) died in the neonatal period (all 4 within 7 days of disease onset). Of those that survived the neonatal period, 40% (6/15) had neurological and/or neurodevelopmental impairment at follow-up; 2 had developmental delay, 1 had hypertonia and a divergent squint, 1 had epilepsy, 1 had hydrocephalus requiring shunting and 1 had severe cerebral palsy who died at age 7 years.

Neonatal Results - Probable Cases

There were 2 reported probable cases of neonatal listeriosis.

One was born at 27 gestation weeks via emergency caesarean-section following maternal pyrexia and pathological fetal cardiotocography, and presented with respiratory distress, lethargy, bradycardia and raised inflammatory markers. The empiric treatment included a penicillin but the neonate died on day 6. *Listeria monocytogenes* was isolated from the maternal blood culture.

The other was born at 30 weeks gestation via emergency caesarean-section following maternal pyrexia, preterm rupture of membrane and pathological fetal cardiotocography, and presented with a rash, respiratory distress and raised inflammatory markers. This neonate was treated with a 21-day course of penicillin and survived the neonatal period with no neurological impairment at follow up. *L. monocytogenes* was cultured from the maternal vaginal swab.

Discussion

The study has highlighted some important lessons for clinicians and public health specialists.

The overall incidence of neonatal listeriosis in our study population was 3.4 per 100,000 live births. This is lower when compared to other countries; for example in the United States of America the incidence of neonatal listeriosis is 8.6 per 100,000 live births [15] and in Israel it is up to 25.5 per 100,000 live births [16]. Neonatal listeriosis is also rarer when compared to the more common cause

of neonatal infection, such as Group B streptococcal infection, with an incidence of 72 per 100,000 live births [17]. Therefore, neonatal listeriosis remains to be a rare disease. However, the case-fatality rate of neonatal listeriosis remains high; in our case series this was 21% (24% if probable cases were included) whereas the more common Group B streptococcal infection has a lower fatality rate (9.7%) [17]. Therefore, despite its rarity, improvements in the recognition and prevention of listeriosis need to be identified.

There is little scope for improvement in the choice or speed of therapy for neonates, as the vast majority with early-onset infection received penicillin empirically (95%, 18/19) within the first 2 hours (83%, 10/12). This may reflect the targeted use of antibiotics to prevent early-onset group B streptococcal infections, which has also been suggested in a recent study to have a possible role in the reduction of neonatal listeriosis [11]. Of the 4 neonates who died from listerial infection, all received a penicillin and gentamicin empirically, of which 2/3 of those who received benzylpenicillin were switched onto amoxicillin within 24 hours of life following the culture of *L. monocytogenes*. Of the 6 neonates with neurological and/or neurodevelopmental impairment at follow-up, only 1 received a cephalosporin empirically.

Of the 4 mothers of the neonates who died of listerial infection, 2 (50%) did not receive antepartum antibiotics and 2 (50%) received cephalosporins. This might suggest that there is a worse outcome in neonatal listeriosis with mothers who were not treated or inadequately treated.

We found that the majority (95%) of mothers presented with non-specific clinical features. This may be the reason why a significant proportion were not investigated and subsequently not treated as puerperal infection. The most common feature in mothers who were not investigated and treated (no culture performed on any sterile site and no antibiotics commenced) is reduce foetal movement (63%, 5/8), which is not a feature recognised to be associated with puerperal infection [10]. Therefore a lower threshold for screening of puerperal sepsis may not be the solution. However, the choice of empiric treatment for puerperal sepsis can be improved to follow the national guidance, which is designed to treat listeria along with more common bacterial causes in puerperal sepsis. The Royal College of Obstetricians and Gynaecologists (RCOG) has published a guideline on the management of sepsis in the puerperium (accredited by NICE guidelines) which includes guidance on empiric antimicrobials; cephalosporins were not part of the suggested regimens and a combination of clindamycin with either piperacillin/tazobactam or a carbapenem was recommended to provide a broad cover for severe sepsis [10].

The study suggests a disproportionately high representation of Asian and Afro-Caribbean women with listeriosis in England, as highlighted in the literature [5]. Studies into better understanding of the ethnicities and dietary characteristics may point towards those at high risk of the disease to implement strategies at preventing pregnancy-associated listeriosis. This will also provide further valuable information on how to effectively tailor communication strategies, with the help of public health specialists.

There are limitations in this study. Although the data collection in the neonIN database is prospective, participants also gathered additional information retrospectively which resulted in some data being incomplete such as maternal ethnicity. This acknowledged, Afro-Caribbean women remained over-represented in our sample when compared to the national average in England. As a consequence of the data being derived from an on-going survey, the follow-up period of the children was not homogenous. In addition, this study is limited to the units participating in the neonIN surveillance database. However, we believe that the neonIN data are representative of the national neonatal listeriosis as is the case for group B streptococcus in a previous study [3]. A prospective national epidemiological study, such as a British Paediatric Surveillance Unit (BPSU) study could offer a more complete and unbiased perspective.

Tables

Table 1: Maternal Results

Case	Maternal Age	Ethnicity	Symptom/Sign(s)	Labour Complications	Mec.-stained Liquor	Initial WCC (10 ⁹ /L)	Initial CRP (mg/L)	Source of +ve Culture	Diagnosis	Pre-delivery Antibiotic(s)
1	37	Afro-Caribbean	↓ fetal movements	APH, suboptimal CTG	Yes	21.5	94	Blood	Septicaemia	Ciprofloxacin, benzylpenicillin
2	29	Afro-Caribbean	Preterm labour, pyrexia, abdo. pain	Suboptimal CTG	Yes	7.6	144	Blood	Septicaemia	Cefuroxime, metronidazole
3	32	NR	Preterm labour	None	No	NP	NP	NP	None	None
4	29	NR	Preterm labour, pyrexia, abdo. pain, diarrhoea, vag. bleed	APH, suboptimal CTG	No	30	NP	NI	Septicaemia, chorioamnionitis	None
5	29	NR	Flu-like symptoms	None	Yes	NP	NP	NP	None	None
6	21	NR	Preterm labour, ↓ fetal movements, preterm ROM	Suboptimal CTG	Yes	34.3	4	NI	None	None
7	34	NR	↓ fetal movements	Suboptimal CTG	No	NP	NP	NP	None	None
8	24	NR	Preterm labour	None	Yes	NP	NP	NP	None	None
9	29	NR	Preterm labour, ↓ fetal movements	None	Yes	28.7	100.2	NP	None	None
10	31	Caucasian	Pyrexia, preterm ROM	Suboptimal CTG	Yes	20.5	23	vag. swab	Chorioamnionitis	Cefuroxime, metronidazole
11	25	Caucasian	Preterm labour	None	Yes	NP	NP	NI	None	None
12	26	Caucasian	Pyrexia	Suboptimal CTG	No	NR	48	Blood	Septicaemia, chorioamnionitis	Cefuroxime, metronidazole
13	34	Caucasian	↓ fetal movements	Suboptimal CTG	Yes	8.1	14	NP	None	None
14	37	Caucasian	Preterm labour, preterm ROM	None	No	21.2	137	Blood	Septicaemia, chorioamnionitis	NR

15	26	Asian	↓ fetal movements	None	Yes	25.6	NP	NP	None	None
16	31	Afro-Caribbean	Preterm labour, preterm ROM, foul-smelling liquor	None	Yes	6.9	22	Placenta	Chorioamnionitis	Amoxicillin
17	21	Caucasian	None	Suboptimal CTG	Yes	16	215	NI	Chorioamnionitis	None
18	42	Caucasian	↓ fetal movements	Suboptimal CTG	No	NP	NP	NP	None	None
19	25	Asian	↓ fetal movements	Suboptimal CTG	Yes	14.1	17	NI	None	None
20	40	Asian	Preterm labour, pyrexia, flu-like symptoms, vag. bleed	Suboptimal CTG	Yes	23.8	122	Placenta	Chorioamnionitis	Cephalexin, metronidazole
21	27	Afro-Caribbean	Preterm labour, pyrexia	Suboptimal CTG	No	21.3	NR	NR	NR	NR

NR, not recorded; ↓, reduced; abdo., abdominal; vag., vaginal; ROM, rupture of membrane; APH, antepartum haemorrhage; CTG, cardiotocography; Em. CS, emergency caesarean section; SVD, spontaneous vaginal delivery; Mec, meconium; NP, not performed; NI, not isolated; WCC, white cell count; CRP, C-reactive protein; +ve, positive;

Table 2: Neonatal Results

Case	Birth Weight(g)	Gestation (weeks)	5 min Apgar	Symptom/ Sign(s)	Maximum Respiratory Support	Inotropic Support	Peak CRP (mg/L)	Diagnosis	Source of culture	LP	Empiric Antibiotic(s)	Antibiotics Onset (hours post birth)	Length of Antibiotic(s) (days)	Neurological Outcome at Follow-up	Death within Neonatal Period
1	1260	29	5	Resp. distress, rash, hypoglycaemia	IV	Yes	112	Septicaemia	Blood	NP	Amoxicillin, gentamicin	NR	1 (until death)	NA	Yes
2	2860	38	5	Resp. distress	IV+NO	Yes	>250	Septicaemia	Blood	NP	Benzylpenicillin, gentamicin	NR	NR	NA	Yes
3	1835	33	3	Resp. distress, lethargy, hypoglycaemia, seizure	IV+NO	Yes	NR	Septicaemia	Blood	NAD	Amoxicillin	NR	21	Epilepsy	No
4	2560	35	8	Resp. distress	NIV	No	104	Septicaemia	Blood, superficial swab	NAD	Benzylpenicillin, gentamicin	2	14	NAD	No
5	2500	38	9	Resp. distress, poor feeding	IV+HFOV+NO	Yes	NR	Septicaemia	Blood	NAD	Benzylpenicillin, gentamicin	22	NR	NA	Yes
6	1310	29	7	Resp. distress, lethargy, bradycardia, seizure	IV	Yes	87	Septicaemia, meningitis	Blood	NP	Benzylpenicillin, gentamicin	1	3 (until death)	NA	Yes
7	3210	36	9	None	None	No	40	Septicaemia	Blood	Bloody tap	Benzylpenicillin	28	14	NAD	No
8	1070	27	5	Resp. distress	IV	No	71	Septicaemia	Blood	Bloody tap	Benzylpenicillin, gentamicin	2	21	NAD	No
9	1765	32	8	Resp. distress, rash, bradycardia, hepatomegaly	IV	No	40	Septicaemia	Blood, superficial swab	*WCC505, 100% lymphocytes, no growth	Benzylpenicillin, amikacin	1	21	NAD	No
#10	1535	30	8	Resp. distress, rash	NIV	No	42	Septicaemia	NI	NP	Benzylpenicillin, gentamicin	NR	21	NAD	No
11	2865	36	9	Pyrexia	None	No	13	Meningitis	CSF	*WCC768, 80% monocytes	Amoxicillin, cefotaxime	10 days	21	NAD	No
#12	700	27	6	Resp. distress, lethargy, bradycardia	IV+HFOV	Yes	31	Septicaemia, pneumonia	NI	NP	Benzylpenicillin, gentamicin	<1	6 (until death)	NA	Yes
13	1960	32	7	Resp. distress, lethargy, bradycardia	IV	No	175	Septicaemia	Blood	NAD	Amoxicillin, gentamicin	NR	14	NAD	No
14	1760	31	7	Resp. distress	IV	No	97	Meningitis	Stool	*WCC2660, 75% polymorphs, no growth	Amoxicillin, cefotaxime	<1	50	Hydrocephalus	No
15	2150	34	6	Resp. distress	None	No	43	Septicaemia	Blood	Bloody tap	Amoxicillin, gentamicin	<1	21	NAD	No
16	1588	30	8	Resp. distress, lethargy, bradycardia	IV	No	126	Septicaemia	Blood	NAD	Amoxicillin, gentamicin	<1	21	Hypertonia & divergent squint	No
17	2800	34	6	Resp. distress	NIV	No	100	Septicaemia	Blood	NP	Amoxicillin, gentamicin	1	21	NR	No
18	2180	34	8	Resp. distress & rash	IV	Yes	208	Septicaemia, meningitis	Blood	NP	Amoxicillin, cefotaxime	<1	21	NAD	No
19	1300	29	5	Resp. distress & lethargy	IV+HFOV+NO	Yes	163	Septicaemia	Blood	NAD	Benzylpenicillin, gentamicin	NR	21	Dev. delay	No
20	2590	35	4	Resp. distress, lethargy, bradycardia	IV+HFOV+NO	Yes	137	Septicaemia, meningitis	Blood, superficial swab	Bloody tap	Cefotaxime	1	21	Dev. delay	No
21	1835	33	3	Seizure & lethargy	IV+NO	Yes	301	Septicaemia, pneumonia	Blood	NAD	Amoxicillin, gentamicin	NR	21	Cerebral palsy	No

Resp. distress, respiratory distress; IV, invasive ventilation; NIV, non-invasive ventilation; HFOV, high-frequency oscillatory ventilation; NO, nitric oxide; NR, not recorded; CRP, C-reactive protein; CSF, cerebrospinal fluid; NI, not isolated; LP, lumbar puncture; NP, not performed; NAD, no abnormality detected; *WCC, white cell count per mm³; #, cases 10 and 12 are probable cases of neonatal listeriosis; NA, not applicable; Dev., developmental;

Contributors Statement

Dr Stefania Vergnano designed and conducted the study, including patient recruitment. Dr Shari Sapuan conducted the data analysis and prepared the manuscript draft with important intellectual input from Dr Stefania Vergnano and Dr Paul Heath. All authors approved the final manuscript. Most authors were involved in the data collection. NeonIN provided statistical support in analysing the data with input from Dr Stefania Vergnano and Dr Christina Kortsalioudaki. Dr Shari Sapuan and Dr Stefania Vergnano had complete access to the study data.

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Conflict of interest

None

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Neonatal Listeriosis in the UK: A 10-year Review

Highlights

- Despite its rarity and the prompt and appropriate use of antibiotics neonatal listeriosis has a high case-fatality rate
- There is room for improvement in the adherence to the national guidance in the choice of empiric antibiotics for puerperal sepsis, which also targets listeriosis
- A better understanding of dietary characteristics based on maternal ethnicities may point towards those at higher risk to implement strategies into preventing pregnancy-associated listeriosis suggested by the disproportionately high representation of Asian and Afro-Caribbean women with listeriosis